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First Named Inventor	TCHAGA, GRIGORIY S.
Group Art Unit	1656
Examiner Name	ROOKE, AGNES BEATA
Attorney Docket Number	CLON-056US2

ENCLOSURES (check all that apply)

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- [ ] After Allowance Communication to Group
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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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Signature	
Date	AUGUST 31, 2007

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REPLY BRIEF Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	10/762,588
	Confirmation Number	3721
	Attorney Docket No.	CLON-056US2
	Filing Date	January 21, 2004
	First Named Inventor	Tchaga, Grigoriy
	Examiner	Rooke, Agnes
	Group Art	1656
	Title: *Methods and Compositions for Protein Purification*	

Sir:

This Reply Brief is in response to the Examiner's Answer mailed by the Office on July 3, 2007.

Please charge any required fees to Deposit Account No. 50-0815, order number CLON-056US2.

REPLY BRIEF

In this Reply Brief, the Appellants address several issues raised in the Examiner's Answer. The Appellants note that all arguments presented in the prior Appeal Brief still apply with equal force, but are not reiterated here solely in the interest of brevity and for the convenience of the Board.

In this Reply Brief, the Appellants address specific assertions made by the Examiner in responding to Appellants' arguments. The Examiner's assertions are addressed in two sections below, each section representing a separate and independent reason why the remaining rejections should be withdrawn.

It is noted that in the Appeal Brief of February 6, 2007, the Appellants chose to argue the claims in six groups, specifically, Group I, consisting of Claims 11, 16 and 23; Group II, consisting of Claim 12; Group III, consisting of Claim 13; Group IV, consisting of Claims 18, 21 and 24; Group V, consisting of Claim 19; and Group VI, consisting of Claim 20.

In the Examiner's Answer of July 3, 2007, the Examiner elects to respond to the Appellants' arguments in two groupings: a set of claims 11-13, 16, and 23 and another set of claims 18-21 and 24 "for purposes of clarity and because the same issues and the same arguments are being presented for each of those 6 groups" (Examiner's Answer, page 6).

Appellants will respond to Examiner's arguments according to the Examiner's elected format; Appellants respectfully emphasize, however, that although Examiner asserts that the six claim groups present "the same issues and the same arguments," Appellants disagree. The argument of the claims as six groups was grounded in the identity and ordering of metal resins in tandem columns (i.e., hard vs. intermediate ions in the first column), since such resin identity and ordering is specifically recited by the

claims. Tchaga teaches a single column; whereas Porath teaches tandem columns, but teaches the use of Ni(II) and Fe(III) resins **only**. On this basis, Appellants submit that Examiner's arguments do not address the independent issues raised by each claim group in the Appeal Brief, namely, that the instant Application discloses specific ordering of the use of resins, which orders are not disclosed by the cited art.

Response to Examiner's argument addressing currently rejected claims 11-13, 16 and 23.

As discussed in the Appeal Brief, the claims are directed to, *inter alia*, a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized metal ion; a second composition including a second metal ion chelate resin including a second immobilized metal ion; and a recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for the metal ion affinity peptide.

The claims stand rejected as obvious over Tchaga *et al.* (hereinafter "Tchaga," WO 99/57992) in view of Porath *et al.* (hereinafter "Porath," Biochemistry, 1983: 22; p.1621-1630).

In the Appeal Brief, the Appellants argued that while Tchaga et al. is directed to the purification of a protein of interest using ion affinity tags, in which the affinity of the fusion protein for the chromatographic column is mediated entirely by the metal ion binding capacity of the affinity tag itself, Porath et al. is directed to the purification of polypeptides to which no ion affinity tag has been fused, such that the purification process taught by Porath et al. depends entirely upon the affinity of various features of the native polypeptide sequence itself for the ion-loaded column.

Furthermore, the binding sites of the immobilized metal ion of the first column are not the same as the binding sites of the immobilized metal ion in the second column. In fact the immobilized metal ion of the first column binds a number of distinct proteins, whereas the metal ion of the second column binds a distinct subset of other proteins. In other words, the goal of the separation procedure as described by Porath et al. is to separate wild type proteins into separate and distinct subset groups of proteins.

The goal of Tchaga's invention is to utilize the same short polypeptide recombinant fusion sequence to combine the separation selectivity ***of both*** immobilized metal ions by consequent binding of the target fusion protein via the above mentioned purification tag first to the first immobilized metal ion column ***and then*** to the second immobilized metal ion column in a single chromatographic step.

As such, the ordinarily skilled artisan would find no reason to combine the teachings of Tchaga et al. with those of Porath et al., since there is no reason to expect that a method directed to the purification of untagged proteins would provide an improvement in the purification of ion binding peptide-tagged proteins. The only document of record which teaches the success of such an approach is the instant Application.

On page 7 of the Examiner's Answer in the final two paragraphs, the Examiner first reiterates the prior rejection and further responds that "there is no teaching in Tchaga et al. or Porath et al. that the metal ion chelate resin will distinguish between native and tagged proteins, since even though polyhistidine tags bind strongly to divalent metal ion[s], particularly nickel, the metal ion chelate resin can also be used for natural proteins that have inherent affinity for divalent or trivalent cations, such as Ni(II) and Fe(III) as taught by Porath. Thus, tagged and untagged proteins can be used for immobilization and purification with metal ion chelate resins because of their structural affinity to the positively charged metal ion."

The Appellants reply that the Examiner's response is not apposite to the issue at hand, which is one of the motivation which the Examiner is required to provide; specifically, why one of skill would be motivated to apply a two-column method taught for use with native proteins to an ion-binding tagged protein taught as purified with a single column. The Examiner fails to address Appellants' argument that the point of including a designed ion-binding tag sequence is to introduce an artificial binding moiety precisely so as to be rid of the effects of "inherent affinity," as explicitly taught by Tchaga, which states:

> "There are numerous advantages of using a high affinity fusion protein. For example, **the use of an affinity peptide ensures that no part of the native protein of interest is involved in adsorption – the binding between the fusion protein and the ligand**. At the same time, extremely high selectivity in the adsorption process is achieved." (Tchaga et al., page 2, lines 15-20)

As such, the methods of Tchaga and Porath address two distinct problems: Tchaga et al. that of using and maximizing the ion affinity of a polypeptide sequence specifically designed to bind metal ions (Tchaga et al., page 2, lines 15-20), and Porath et al. that of optimizing column conditions to isolate proteins whose metal-binding determinants are variable or unknown (Porath et al., page 1628, paragraph 8; page 1629, left column).

Therefore, the ordinarily skilled artisan finds no motivation to combine the references, as discussed. If the motivation is not present in the references, then Examiner must provide extrinsic evidence that such motivation is found in knowledge generally available in the art or based upon established scientific principles. No such evidence is provided in any Office communication of record.

Recently, in *KSR v. Teleflex,*[1] the Supreme Court reviewed the "teaching, suggestion, motivation" (TSM) test for establishing a *prima facie* case of obviousness. While the Court warned against its "rigid application",[2] the Court also found that the TSM test could provide a "helpful insight" in determining whether the claimed subject matter is obvious under §103(a).[3] Even when one steps away from the application of the TSM test as routinely applied prior to *KSR v. Teleflex*, and turns instead to the Court's guidance regarding the case, the obviousness rejection still fails to meet the necessary criteria. When considering the Federal Circuit's application of the "obvious to try" standard to the adjustable gas pedal invention at issue, the Court stated:[4]

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

(emphasis added)

As set out above, the present rejection is based on the assertion that the skilled artisan would be motivated to modify a method directed to the purification of untagged proteins so as to provide an improvement in the purification of ion binding peptide-tagged proteins. Yet this solution proposed by the Office is not supported by any evidence that this is a "predictable variation" of the protocol of Tchaga, or a "predictable solution" to any "problem" identified by the Office. Moreover, there is also no evidence that the Office's proposed modification of Tchaga has been used in a similar method and thus the skilled person "would recognize that it would improve [the method] in the

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1 *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (U.S. 2007).
2 *KSR*, slip op. at 15.
3 *KSR* slip op. at 14. *See also*, Memorandum to Technology Directors from Margaret A. Focarino, Deputy Commissioner for Patent Operations, May 3, 2007.
4 *KSR*, slip op. at 17.

same way." Indeed, the Appellants wish to emphasize that the cited references are directed to two different strategies of protein purification which were not combined in any document of record from the period of 1983 to 1998 for the reason that one of skill in the art had no reason to expect success in applying a strategy for purifying untagged proteins to a method teaching the use and optimization of ion-binding tags. Unlike the situation in *KSR*, the field of the claimed invention is one that is not as predictable as moving the position of a sensor in a mechanical device.

On page 8 of the Examiner's Answer, second line, the Examiner further asserts that "both references deal directly with the same area of endeavor, that is, the art of protein purification, and the fact that Porath et al, take advantage of the properties that the protein to be purified already has and Tchaga et al. add the desired properties is no practical difference at all."

However, Appellants respectfully note that in the Advisory Action of November 27, 2006, the Examiner states that "the tagged status of the protein **is relevant** because it will dictate a proper choice of a column and a buffer (i.e. for tagged proteins a column with immobilized nickel ions in a resin is most appropriate, for example)" (Emphasis added).

Appellants concur, and note that the addition of an ion-binding tag does far more than merely "add the desired properties," as asserted by the Examiner in the most recent communication. Again, as explicitly taught by Tchaga itself, the addition of the ion-binding tag **removes entirely** from consideration the properties of the protein to be purified by ensuring that "no part of the native protein of interest is involved in adsorption" (Tchaga, page 2, lines 17-18).

As such, and given the breadth and unpredictability of the art of protein purification, there is no motivation to combine the references in the manner suggested

by the Examiner since the references are directed to the purification of different types of proteins and there is no evidence provided that applying Porath's method to the purification of Tchaga's tagged proteins would provide any benefit such that one would be motivated to make the Examiner-suggested combination of teachings.

Thus, the Appellants prior arguments still stand with equal force. The Appellants submit that all remaining rejections may be withdrawn on this basis alone.

Response to Examiner's argument addressing currently rejected claims 18-21 and 24.

In addition to the above argument, the Applicants have also argued that Tchaga et al. teach the purification of an ion-tagged affinity protein with a single column, whereas Tchaga et al. are silent with regard to the use of more than one column, and therefore are silent with regard to the biophysical characteristics, identity or order of any particular pair of metal ions to be used a system of tandem columns.

On pages 9 and 10 of the Examiner's Answer, the Examiner alleges that since the combined references taken together teach all of the metal ions taught in the present Application, that the references teach all of the limitations of Claim 18 and the dependent claims. The Examiner states that Porath et al. did not teach away from other metals such as Co(II) and further alleges that Co(II) is an art-recognized equivalent for other metals as taught by Tchaga.

Appellants reply, however, that provision of a mere laundry list of different metal ions, in the absence of teaching away, does not exhaust the limitations of the instant claims, which recite specific identities, properties, and ordering of metal resins in tandem columns (i.e., hard vs. intermediate ions in the first column; specific residues in

the first and/or second columns). Tchaga teaches a single column; whereas Porath teaches tandem columns, but teaches the use of Ni(II) and Fe(III) resins **only**. On this basis, Appellants submit that, as discussed above, Examiner's arguments do not address the independent issues raised by each of the claim groups as argued in the Appeal Brief, namely, that the instant claims recite specific identities, properties, and ordering for the use of resins, which orders are not disclosed or suggested by the cited art.

Thus, the Examiner's argument in the Reply Brief is ungrounded and, as such, the Appellants' prior arguments still stand with equal force.

In view of the foregoing discussion, the Applicants request that all remaining rejections be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: August 31, 2007

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